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US006180370B1

(12) **United States Patent**
Queen et al.

(10) **Patent No.: US 6,180,370 B1**
(45) **Date of Patent: *Jan. 30, 2001**

(54) **HUMANIZED IMMUNOGLOBULINS AND METHODS OF MAKING THE SAME**

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(73) Assignee: **Protein Design Labs, Inc.**, Fremont, CA (US)

(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **08/484,537**

(22) Filed: **Jun. 7, 1995**

Related U.S. Application Data

(63) Continuation-in-part of application No. 07/634,278, filed on Dec. 19, 1990, now Pat. No. 5,530,101, which is a continuation-in-part of application No. 07/590,274, filed on Sep. 28, 1990, now abandoned, which is a continuation-in-part of application No. 07/310,252, filed on Feb. 13, 1989, now abandoned, which is a continuation-in-part of application No. 07/290,975, filed on Dec. 28, 1988, now abandoned.

(51) **Int. Cl.**[7] **A61K 39/395**
(52) **U.S. Cl.** **435/69.6**; 435/172.3; 435/328; 530/387.3; 530/388.2; 424/133.1; 424/143.1
(58) **Field of Search** 424/133.1, 143.1; 435/328, 69.6, 172.3; 530/387.3, 388.2

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(57) **ABSTRACT**

Novel methods for producing, and compositions of, humanized immunoglobulins having one or more complementarity determining regions (CDR's) and possible additional amino acids from a donor immunoglobulin and a framework region from an accepting human immunoglobulin are provided. Each humanized immunoglobulin chain will usually comprise, in addition to the CDR's, amino acids from the donor immunoglobulin framework that are, e.g., capable of interacting with the CDR's to effect binding affinity, such as one or more amino acids which are immediately adjacent to a CDR in the donor immunoglobulin or those within about about 3 Å as predicted by molecular modeling. The heavy and light chains may each be designed by using any one or all of various position criteria. When combined into an intact antibody, the humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen, such as a protein or other compound containing an epitope.

30 Claims, 55 Drawing Sheets